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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/629,859	07/30/2003	Gary F. Gerard	0942.5530002/RWE/HCC	6152

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STERNE, KESSLER, GOLDSTEIN & FOX PLLC
1100 NEW YORK AVENUE, N.W.
WASHINGTON, DC 20005

EXAMINER	
RIGGINS, PATRICK S	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 12/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/629,859	GERARD, GARY F.	
	Examiner	Art Unit	
	Patrick S. Riggins	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/2/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

Election/Restrictions

1. Receipt is acknowledged of an Election filed 9/21/05, in which applicant elected group II, claims 13-20 with traverse. The search of the elected group revealed that this was indeed coextensive with that required for group I, claims 1-12 and 21-24. As such the restriction requirement is withdrawn and groups I and II are rejoined. Thus, after this rejoinder claims 1-24 are pending and under examination.

Specification

2. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

3. The use of the trademarks RNASEOUT, SUPERASE-IN, SUPERSCRIPT, SUPERSCRIPT II, THERMOSCRIPT, FLUOROSCRIPT, and GATEWAY has been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

4. The disclosure is objected to because of the following informalities: The sequence present on page 45 requires a sequence identifier. See the attached Notice to Comply.

Appropriate correction is required.

Claim Objections

5. Claims 18 and 24 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

6. Claim 18 is drawn to a cDNA molecule according to claim 17, while claim 17 is also drawn to the same cDNA molecule.

7. Claim 23 is drawn to reaction mixture while claim 24 is drawn to a composition both of which comprise identical components. The reaction mixture of claim 23 is a composition and the composition is indeed a reaction mixture.

8. Claims 14-18, 20, 23, and 24 are objected to because of the following informalities: claim 14 depends from itself and as such is improper. As claims 15-18 each ultimately depend from claim 14 as well, they are similarly objected to. Claim 20 depends from itself and is thus improper. Claims 23 and 24 both misspell micromolar as "micomolar". Appropriate correction is required.

9. In the interest of compact prosecution, for the remainder of this Office Action claim 14 will be read to depend from claim 13 and claim 20 will be read to depend from claim 19.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 10-13, 18-20, and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

12. Claims 10-12 each recite the limitation "The composition" as the first two words. There is insufficient antecedent basis for this limitation in the claim. Claim 8 from which each of claims 10-12 depend is not drawn to a composition. In the interest of compact prosecution claims 10 and 11 will be read to depend from claim 9 for the remained of the Office Action.

13. Claim 12 recites the limitation "said polypeptides" in line 1. There is insufficient antecedent basis for this limitation in the claim. In the interest of compact prosecution claim 12 will be read to depend from claim 10 for the remainder of this Office Action.

14. Claim 13 is drawn to a method of reverse transcription yet step recites (a) "nucleic acid" template, while step (b) recites that a complementary "nucleic acid" is produced. By definition reverse transcription is the transcription of RNA into DNA. Thus the template of step (a) must be RNA and the product of step (b) must be DNA. The recitation of the broad "nucleic acid" limitation renders the claim indefinite because the skilled artisan would not understand the metes and bounds of the limitations as all prior knowledge would suggest RNA and DNA, while the claim would seem to encompass more than this. The limitations of claim 14 correct this deficiency.

15. Claim 18 is drawn to a cDNA molecule created by the method of claim 17. Claim 17 is not a method claim. It is thus unclear what the metes and bound of claim 18 are intended to encompass.

16. Claim 19 is drawn to a method of amplifying a "nucleic acid" template, yet a polypeptide possessing RT activity is included in the mixture. It is unclear what purpose this polypeptide would serve unless the template was RNA. As such the skilled artisan could not determine the metes and bounds of this claim.

17. Claim 20, which depends from claim 19 for the purposes of examination does not correct this indefiniteness and is thus indefinite as well.

18. Claim 22 recites "terminating agents" but there is no proper definition of this term in the specification. As such the skilled artisan would be unable to ascertain the metes and bounds of this limitation.

19. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

20. Claims 1-5, 9, and 13-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibitors consisting of nucleotides or chelating agents, compositions comprising these nucleotides or chelators, methods of using these nucleotides or chelators, the products made by these methods, and kits comprising these nucleotides or chelators does not reasonably provide enablement for any other of the embodiments of the inhibitors disclosed in the specification including but not limited to: anions, basic salts, amino acids, and polyamino acids 20 amino acids in length or shorter. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

21. The claims are drawn to inhibitors defined in the specification at page 17, last paragraph as "any compound or molecule or composition (or combination of the same or different molecules, compounds or compositions) that inhibits, prevents, substantially reduces or eliminates degradation or cleavage of RNA". These inhibitors can be any compound including but not limited to those compounds listed in paragraph 20 above. To practice the full scope of the claimed invention, the skilled artisan would be required to perform an undue level of experimentation.

22. A number of factors have been considered in making this assertion that undue experimentation is required to practice this invention as delineated by In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

23. The claims are nearly infinite in breadth as essentially any compound could theoretically serve the purpose set forth fro the inhibitor. The specification does indeed indicate however that the predominant embodiments contemplated are those recited above in paragraph 20.

24. AbouHaidar (Z Naturforsch 54c: 542-548 (1999), newly cited) observed that Mg^{2+} lead to the degradation of RNA and that chelators EDTA and citrate lead to the stabilization of RNA (see page 544, Results first paragraph and page 545, Inhibitors, first paragraph). Further the specification teaches that EDTA and 4mM dNTPs can lead to the stabilization of RNA (see Figure 3). The art of record and the specification are silent with regard to the ability of anions,

basic salts, or amino acids to stabilize RNA. Indeed the specification only exemplifies EDTA and dNTPs, the assertion that any other of the described embodiments for the inhibitor are all mere allegations with no scientific evidence presented or of recor5d in the prior art to suggest that any of anions, basic salts, or amino acids could prevent the Mg^{2+}-mediated degradation of RNA. Further, it is standard practice (as cited below) to include anions in a reverse transcriptase (RT) reaction. Indeed the predominant form of Mg^{2+} used in RT is supplied as $MgCl_2$. Thus, even with no addition of any other source of anions, Cl^- is in a 2-fold molar excess over Mg^{2+} simply from this source of $MgCl_2$. Thus, even if anions including Cl^- were able to act as inhibitors of the invention, it is unclear how this could possibly be free of the prior art.

25. As stated above, the specification only provides support for the assertion that these various molecules and compounds act as inhibitors of the invention is through the exemplification that dNTPs and EDTA can lead to the stabilization of RNA. The other possible inhibitor embodiments are support only through allegation.

26. Therefore, in order to use any molecule aside from dNTPs and chelators the skilled artisan would be required to test each and every possible embodiment through trial and error-type experimentation. This is the antithesis of a properly enabling disclosure, as any embodiment aside from those exemplified would require experimentation. It is thus concluded that the skilled artisan would be forced to perform an undue level of experimentation in order to practice the full scope of the claimed invention.

Claim Rejections - 35 USC § 102

27. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

28. Claims 1-24 are rejected under 35 U.S.C. 102(b) as being anticipated by Schwabe (FOCUS 20: 30-33 (1998), newly cited).

29. The claims are drawn to an inhibitor that optionally has a negative charge, is not a ribonuclease inhibitor, is not a protease, is a chemical compound, is one or more nucleotides, and can interact with a degradation component that can be Mg^{2+}. The claims are further drawn to a composition comprising one or more inhibitors and one or more degradation components, which can optionally further comprise polypeptides with RT activity that can optionally have reduced RNase H activity, and can be selected from a group of many different RTs. The claims are further drawn to a method for reverse transcription comprising mixing one or more nucleic acid templates with one or more inhibitors and one or more polypeptides having RT activity and incubating this mixture under conditions sufficient to make a cDNA first strand. The nucleic acid can be an mRNA, poly A+ RNA, or population of mRNAs. The mixture can be incubated at a temperature ranging between 40°C and 75°C. The method can further comprise incubating under conditions sufficient to allow second strand synthesis. The claims are further drawn to a method to amplify nucleic acids comprising mixing a nucleic acid template with one or more inhibitors, one or more polypeptides having RT activity, and one or more DNA polymerases, and incubating under conditions to allow for amplification of the template. The claims are further

drawn to cDNAs made by these methods. The claims are further drawn to a kit comprising one or more inhibitors and optionally further comprising one or more of nucleotides, DNA polymerases, buffers primers, host cells or terminating agents. Finally the claims are drawn to a reaction mixture or a composition comprising an inhibitor at at least 4000 micromolar (i.e. 4 millimolar (mM)) of an inhibitor and one or more mRNA templates.

30. Schwabe discloses a method for first strand synthesis from an mRNA template and subsequent PCR amplification of this which necessarily comprises second strand synthesis. In first strand synthesis, Schwabe includes Tris acetate, potassium acetate, and magnesium acetate (of which the acetate is an anion), 1 mM of each nucleotide, which when considered collectively constitutes 4 mM total of all dNTPs (See page 30 column 2 second paragraph). RNA isolated from HeLa cells or rat brain were used with oligo dT as the primer for first strand synthesis (see page 30, first column last paragraph and page 31 first column, top). PCR was performed to amplify the cDNA produced (page 31, first column, first full paragraph).

31. Thus Schwabe discloses nucleotides, defined by the specification as inhibitors, in composition with Mg^{2+} and an avian RT with reduce RNase activity (page 30, first column, first paragraph). The first strand synthesis is carried out at temperatures ranging from 42-58°C (see Figure 2). Schwabe also essentially discloses a kit comprising inhibitors, i.e. dNTPs, nucleotides, a DNA polymerase, buffers, and primers. Further the reaction mixture of Schwabe comprises 4 mM dNTPs and mRNA templates comprised within the total RNA used. Thus each claim is anticipated by Schwabe.

32. Claims 1-10, 12-15, 17, 18, and 22-24 are rejected under 35 U.S.C. 102(b) as being anticipated by Krug (Methods Enzymol 152: 316-325 (1987), newly cited).

33. Krug discloses a method for first stand synthesis where a poly A+ RNA template is used with RT buffers, which comprise Mg^{2+}, dNTPs, the polyanion spermidine, sodium pyrophosphate, recognized by the specification as a chelator, and either AMV RT or MMLV RT (see the table on page 322). As 4 μl of a stock of 10 mM each of dNTPs was added to a 40 μl reaction, the concentration of each dNTP in the reaction was 1 mM. Thus with the four nucleotides present, the total dNTP concentration in the reaction was 4 mM. In the case of AMV, the reaction was incubated at 42°C. Thus Krug discloses the inhibitors of dNTPs and pyrophosphate (and additionally the spermidine). Further Krug's reaction is a composition comprising mRNA, 4mM dNTPs, pyrophosphate, RT, primers, Mg^{2+}, and the RT is from AMV or MMLV. Thus Krug anticipates each of claims 1-15, 17, 18, and 22-24.

34. Claims 1-24 are rejected under 35 U.S.C. 102(b) as being anticipated by Gerard (Mol Biotechnol 8: 61-77 (1997), newly cited).

35. Gerard discloses methods and reagents for first strand synthesis, second strand synthesis, and RT-PCR. Gerard discloses the use of Pyrophosphate, dNTPs, spermidine, and EDTA in first strand reactions (see page 66, first column, and Figure 2, top-right panel). With AMV RT, Gerard uses 1 mM dNTPs, which is 4 mM considered collectively, sodium pyrophosphate, and spermidine (see Table 3). Also in Table 3 Gerard discloses the use of an RNase H negative RT. Further Gerard discloses second strand synthesis (Section 1.2) and RT-PCR (section 1.3).

36. Thus Gerard discloses the inhibitors of dNTPs and pyrophosphate in composition with RNA template, primers, RT that is either rAMV or MLV-derived. The composition further comprises Mg^{2+}. Further Gerard discloses a composition comprising dNTPs, RT, and EDTA (Figure 2, upper right panel). Thus Gerard anticipated each of claims 1-24.

37. Claims 1-8, 21, and 22 are rejected under 35 U.S.C. 102(b) based upon a public use or sale of the invention as evidence by Gibco (Gibco BRL 1997/1998 Products & Reference Guide).

38. Gibco on page 17-1 discloses the sale of dNTPs, which are recognized by the specification as an inhibitor capable of binding Mg^{2+}. Gibco further discloses on page 19-31 the sale of a kit comprising nucleotides, Taq polymerase, termination nucleotides, a sequencing primer, and a buffer. Thus, Gibco anticipates each of claims 1-8, 21, and 22.

Conclusion

39. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick S. Riggins whose telephone number is (571) 272-6102. The examiner can normally be reached on M-F 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patrick Riggins, Ph.D.
Examiner
Art Unit 1633

DAVE TRONG NGUYEN
SUPERVISORY PATENT EXAMINER

Notice to Comply	Application No.	Applicant(s)	
	10/629,859	GERARD, GARY F.	
	Examiner	Art Unit	
	Patrick S. Riggins	1633	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set in the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☒ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☒ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☐ 7. Other: .

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the application**.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (571) 272-2510
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